Docket No. PRD2166USPCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Marc Karel Jozef Francois	Confirmation No: 1592
Serial No.	:	10/585,754	Art Unit: 1624
Filed	:	July 12, 2006	Examiner: Adam C. Milligan
For	:	MITRATAPIDE ORAL SOLUTION	

The Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 CFR § 41.37

Dear Sir:

This Appeal Brief is in response to the Final Office Action mailed November 23, 2009. A Notice of Appeal and Request for Pre-Appeal Brief were filed on February 22, 2010. A Notice of Panel Decision from Pre-Appeal Brief Review was issued on April 2, 2010, informing Appellants that the request was not persuasive and that the time period for filing an Appeal Brief was reset to the later of one month from that notice or two months from the date the Notice of Appeal was filed. Since one month from the notice is the later date, this Appeal Brief was originally due on May 2, 2010. Since this Appeal Brief is being filed on or before August 2, 2010, with a three month extension of time, it is timely.

I. Real Party in Interest

The real party in interest is Janssen Pharmaceutica N.V. to which the inventors have assigned their rights and which is a subsidiary of Johnson & Johnson.

II. Related Appeals and Interferences

None.

III. Status of Claims

Rejected: Claims 1 and 3-12

Allowed: None

Withdrawn: Claim 13

Objected to: None

Cancelled: Claim 2

Appealed: Claims 1 and 3-12

IV. Status of Amendments

No amendments were filed after the Final Office Action of November 23, 2009.

V. Summary of Claimed Subject Matter

The following summary is for the purpose of complying with the provisions of 37 C.F.R. § 41.37(c)(1)(v). The entire disclosure should be reviewed to obtain a complete understanding of the claim language.

Claim 1

Claim feature	Citations to specification
An oral solution comprising mitratapide or a pharmaceutically acceptable salt thereof,	Paragraphs [0002], [0010], [0011]
a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C,	Paragraphs [0010], [0012]-[0015]
a taste modifying agent	Paragraph [0010], [0017], [0018]
and an antioxidant,	Paragraphs [0010], [0020]-[0022]
wherein the pharmaceutically acceptable solvent is selected from the group consisting of dimethyl isosorbide,	Paragraphs [0012]-[0014]

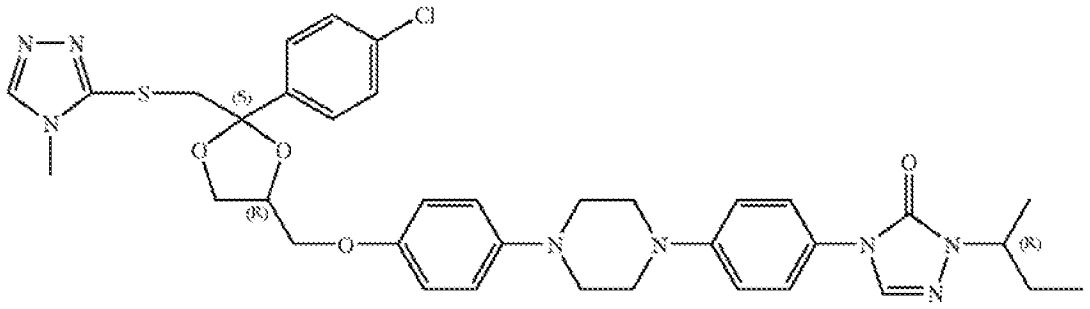
diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glyceride, propylene glycol monolaurate, polyethyleneglycol 200, polyethyleneglycol 300 and polyethyleneglycol 400, and mixtures thereof, or mixtures of polyethylene glycols (PEGs) having an average molecular weight higher than 400 with PEGs having an average molecular weight lower than 400	
so that the mixture thereof is liquid at room temperature.	Paragraph [0012]

VI. Grounds of Rejection to be Reviewed

- Claims 1 and 3-12 under 35 U.S.C. §103(a) as being unpatentable over Heeres (WO96/13499) in view of Chen (2002/0147201) and Basit (The Effect of Polyethylene Glycol 400 on Gastrointestinal Transit: Implications for the Formation of Poorly Water Soluble Drugs, Pharmaceutical Research, Volume 18, No. 8, 2001).

VII. Argument

It is believed that a brief review of the technology involved in this appeal would be helpful to the merits panel reviewing this appeal. The claims are directed to an oral solution of mtitrapatide or a pharmaceutically acceptable addition salt thereof. “Mitrapatide is the International Non Proprietary (INN) name for the compound (-)-[2S-[2.alpha.,4.alpha.(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)- -2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methy]-1,3-dioxolan-4-yl]methoxy-]pheny]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-tria- zol-3-one having the following structure.



."

Specification, [0002]. Mitratapide is known and has been indicated to be useful as a lipid lowering compound, *id.*, [0003]-[0004], and has been formulated as an oral solution in the past using a cyclodextrin solubilizing agent. *Id.*, [0007]. However, it was necessary to use high amounts of the solubilizing agent, adjust the pH to 4.0 and use an antimicrobial preservative. *Id.*, [0008]. The resulting oral solutions required a high amount of solubilizing agent and did not meet the requirements of the European Pharmacopoeia for the antimicrobial efficacy test. *Id.*, [0009].

In contrast to those mitratapide oral solutions, the pending claims feature oral solutions of mitratapide using the specified organic solvents "wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C, a taste modifying agent and an antioxidant, fulfill these requirements." Specification, [0010].

A. Separate Argument for Claim 1

i. Legal standards

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073 (Fed. Cir. 1988). In so doing, the examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966). These showings by the examiner are an essential part of complying with the burden of presenting a prima facie case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). If that burden

is met, the burden then shifts to the applicant to overcome the prima facie case with argument and/or evidence. Obviousness is then determined on the basis of the evidence as a whole. *See id.*; *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986); *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984); and *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976). Further, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

ii. Claim construction

"[A]s an initial matter, the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

Here, claim 1 is directed to an oral solution of mitratapide or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C. Claim 1 sets forth that the pharmaceutically acceptable solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glyceride, propylene glycol monolaurate, polyethyleneglycol 200, polyethyleneglycol 300 and polyethyleneglycol 400, and mixtures thereof, or mixtures of polyethylene glycols (PEGs) having an average molecular weight higher than 400 with PEGs having an average molecular weight lower than 400. The specification contains evidence that not every pharmaceutically acceptable solvent will meet the solubility requirement of claim 1. *Id.*, [0013].

iii. Analysis

The Final Office Action of November 23, 2009 (FR) did not contain a statement of a rejection. Rather, that office action only contained the Examiner's rebuttal of the arguments set forth in Appellants' previous response. Thus,

reference is made to the statement of the rejection set forth in the Office Action of March 30, 2009 (OA).

a. **Heeres does not teach an oral solution**

The Examiner mistakenly characterized Heeres as teaching, *inter alia*, "an oral solution comprising 1 mg/ml of mitratapide (page 17, Compound No. 22), a solvent (page 26, example 8), and sucrose as a taste modifying agent (Page 26, Example 8)." OA, page 4. In addition the Examiner also erred with respect to his statement that Heeres can provide "[a]dditional ingredients may be included to aid in the solubility of mitratapide (Page 10, Line 18). *Id.*. The Examiner has misread/over read Heeres in that Heeres does not describe such an oral solution of mitratapide. Rather, the Examiner has cobbled together portions of Heeres that describe various forms into which the described compounds may be formulated without reference to a specific active ingredient with portions of Heeres that identify mitratapide as one such compound in order to form a phantom embodiment that is not explicitly described in the reference. The manner in which the Examiner combined these disclosures is strong evidence that the rejection is based upon the hindsight provided by Appellant's own disclosure.

Specifically, Heeres describes a vast genus of compounds. *Id.*, page 1, line 31-page 5, line 4. Mitratapide is described as one of the species included within that vast genus. *Id., e.g.,* page 18, compound 40.[1] Heeres also describes a laundry list of dosage forms that the compounds of the reference may have, Including oral, rectal and parenteral injection forms. *Id.*, page 10, line 7-page11 line 2. In describing oral dosage forms, Heeres broadly discloses that "any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions" as well as various solid oral dosage

[1] The Examiner mistakenly identifies compound 22 of Heeres as mitratapide (OA, page 4), which appears to be an error in the Examiner's fact finding. Although compound 22 has the same R^1, R^2, R^3 and –X- substituents as mitratapide, it does not have the same stereochemistry or properties as mitratapide, *i.e.*, compound 40.

forms such as tablets and capsules. *Id.*. Heeres does not specifically link this laundry list of dosage forms to mitratapide.

The Examiner relies upon Example 8 of Heeres in support of this phantom embodiment for disclosure of a "solvent" and "sucrose as a taste modifying agent." OA, page 4. Example 8 of Heeres describes specific adjuvants that can be used to form an "oral solution" with an "active ingredient" (A.I.). The A.I. of Example 8 is generically a "compound of formula (I), a N-oxide form, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof." *Id.*, page 26, lines 6-9.[2] It is not clear which of the specific compounds used in Example 8 the Examiner considers to be a "solvent." However, the end result of Example 8 is an aqueous solution. In this regard, reference is again made to Table 1 of the present specification that provides evidence that not every "solvent" will result in the oral solution set forth in claim 1.

Further, the Examiner's fact finding appears to be faulty, as evidenced by the fact that Example 8 does not, as contended, specifically state the presence of sucrose. Rather, the formulation of Example 8 uses sodium saccharin, raspberry and gooseberry essence, which appear to be at least some of the taste modifying agents of that formulation.

However, perhaps the most egregious misstatement of the disclosure of Heeres made by the Examiner is that Heeres describes "[a]dditional ingredients may be included to aid in the solubility of mitratapide," citing to page 10, line 18 of Heeres. OA at page 4. When the entire cited passage is read, it is seen that the Examiner has mischaracterized it. The entire passage reads "[f]or parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included." Obviously this passage has nothing to do with oral dosage forms as alleged by the Examiner. Further, this passage generically describes parenteral dosage forms for injection with a generic active ingredient. This passage does not describe an oral solution with mitratapide as alleged by the Examiner. Heeres

itself recognizes that oral solutions differ from injectable solutions. Compare Example 8: Oral solutions with Example 11, Injectable solution of Heeres where the adjuvants of Example 11 are not coextensive with those of Example 8. Thus it is error on the Examiner's part to mix and match these disparate disclosures of Heeres in an attempt to arrive at the subject matter of claim 1. Moreover, this is further strong evidence of the use of impermissible hindsight.

In response to Appellants' arguments concerning claim 1 being directed to an oral solution, the Examiner dismissed this claim language as a "statement of intended use." FR, page 3. This is error on the part of the Examiner because a functional limitation must be evaluated and considered just like any other limitation of a claim for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. The court's opinion in *In re Stencel*, 828 F.2d 751, 754 (Fed. Cir. 1987) is instructive on this point as the court stated:

> As a matter of claim draftsmanship, appellant is not barred from describing the driver in terms of the structure imposed upon it by the collar having plastically deformable lobes. The framework -- the teachings of the prior art -- against which patentability is measured is not all drivers broadly, but drivers suitable for use in combination with this collar, for the claims themselves are so limited.

The court concluded that "Stencel is not inhibited from claiming his driver, limited by the statement of its purpose, and further defined by the remaining clauses of the claims at issue, when there is no suggestion in the prior art of a driver having the claimed structure and purpose." *Id,* 828 F.2d at 755. In similar manner, Appellants are claiming their composition in part by stating that the composition is an oral solution. It is entirely proper for Appellants to claim the composition in this manner and equally improper for the Examiner to dismiss this aspect of claim 1 as an intended use.

b. Chen does not teach or suggest the addition of PEG 400 to an oral solution comprising mitratapide

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[2] The statement made at page 4 of the response of June 30, 2009, that Example 8 of Heeres teaches an "oral solution comprising mitratapide and a solvent" is incorrect since Example 8 of the reference is not limited to a specific A.I.

Chen describes water soluble and palatable complexes of poorly water soluble pharmaceutically active ingredients where the active ingredient is complexed with glycyrrhizin. *Id.*, [0019], [0035]. Active ingredient is broadly defined and exemplified by a long list of pharmaceutical classes of compounds as well as individual drugs in Chen. *Id.*, [0020],[[0025] [0027] and [0035]. Glycyrrhizin is a naturally occurring flavoring agent found in licorice. *Id.*, [0047].

Chen describes the use of polyethylene glycol as an optional plasticizer and that antioxidants can be used in the formulations of that reference. *Id.*, [0064], [0076].

c. Basit does not teach or suggest the addition of PEG 400 to an oral solution comprising mitratapide

Basit describes the results of studies performed to assess the effect PEG 400 has on the solubility of poorly-water soluble drugs. *Id.,* Title, Abstract. Basit states that PEG 400 is widely used as a solubility-enhancing vehicle for drugs. *Id.*, page 1146, right hand column. This is consistent with Appellants' description of PEG 400 in the specification that PEG 400 is the most widely used pharmaceutically acceptable solvent. *Id.*, [0015].

The Examiner relies upon Basit for its teaching of PEG 400 as a "particularly preferred solubility enhancer…." OA, page 5. *See also* FR, page 3. It is urged that the Examiner has misread/over read Basit. In applying the teachings of Basit, the Examiner has overlooked or ignored statements in Basit that teach away from using PEG 400 with the pharmaceutical agents described in Heeres.

For example, Basit states that "[a]lthough PEG 400 has been widely used in these respects, in some cases the results have been less successful." *Id.* Page 1146, right hand column. In discussing the results from the referenced studies, Basit, indicates that PEG 400 "by means of reducing residence time in the small intestine, is therefore likely to have a detrimental effect on the rate and/or extent of absorption of drugs." *Id.*, page 1149, right hand column. Basit then concludes that, while PEG 400 will improve the solubility of drugs, the

"concurrent reduction in gastrointestinal transit time…may limit the opportunity for drug absorption and nullify any possible bioavailability enhancement. *Id.*.

"[A reference] must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed.Cir.1987). Here, the Examiner has only picked passages from Basit believed to support the rejection and overlooked or ignored passages that lead away from the claimed compositions. This is error on the part of the Examiner. When Basit is considered in its entirety it is seen that the present invention involves an unpredictable art area and it is improper for the Examiner to reach the sweeping conclusions that have resulted in the present rejection.

It is respectfully requested that the rejection of claim 1 be reversed.

B. Claims 3-12

For the purpose of this appeal, claim 3-12 stand or fall based upon claim 1.

Conclusion

For the reasons set forth above, it is believed that the rejection is in error. Appellants respectfully ask the Board to reverse the Examiner's rejection under 35 U.S.C. § 103(a).

Respectfully submitted,

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Dated: July 30, 2010

CLAIMS APPENDIX

1. (Previously Presented) An oral solution comprising mitratapide or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C, a taste modifying agent and an antioxidant, wherein the pharmaceutically acceptable solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glyceride, propylene glycol monolaurate, polyethyleneglycol 200, polyethyleneglycol 300 and polyethyleneglycol 400, and mixtures thereof, or mixtures of polyethylene glycols (PEGs) having an average molecular weight higher than 400 with PEGs having an average molecular weight lower than 400 so that the mixture thereof is liquid at room temperature.

2. (Cancelled)

3. (Previously Presented) An oral solution as claimed in claim 1 wherein the pharmaceutically acceptable solvent is polyethyleneglycol 400.

4. (Previously Presented) An oral solution as claimed in any of claims 1 or 3 wherein the taste modifying agent is an intense sweetener, a bulk sweetener, a flavouring agent, or a taste masking agent.

5. (Previously Presented) An oral solution as claimed in claim 4 wherein the taste modifying agent is an intense sweetener selected from the group consisting of saccharin, aspartame, acesulfame, cyclamate, alitame, a dihydrochalcone sweetener, monellin, neohesperidin, neotame, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), and the pharmaceutically acceptable salts thereof.

6. (Original) An oral solution as claimed in claim 5 wherein the intense sweetener is present in an amount ranging from 0.1 to 10 mg/ml.

7. (Previously Presented) An oral solution as claimed in claim 6 wherein the intense sweetener is sucralose.

8. (Original) An oral solution as claimed in any of claims 1 to 7[3] wherein the antioxidant is selected from the group consisting of BHA, BHT, propyl gallate, DL-ά-tocopherol, and citric acid, and mixtures thereof.

9. (Original) An oral solution as claimed in claim 8 wherein the antioxidant is present in an amount ranging from 0.1 to 10 mg/ml.

10. (Original) An oral solution as claimed in claim 9 wherein the antioxidant is BHA.

11. (Original) An oral solution as claimed in claim 10 comprising 5 mg/ml mitratapide, sucralose in an amount ranging from 0.5 to 5 mg/ml, and BHA in an amount ranging from 1 mg/ml to 5 mg/ml, dissolved in PEG 400.

12. (Original) An oral solution as claimed in claim 11 comprising 5 mg/ml mitratapide, sucralose in an amount of 2 mg/ml, and BHA in an amount of 2 mg/ml, dissolved in PEG 400.

13. (Withdrawn) A process of preparing an oral solution as claimed in any of claims 1 to 12, characterized in that said process comprises the steps of dissolving mitratapide, the taste modifying agent and the antioxidant in the pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C, and stirring until a homogeneous solution is obtained.

[3] It is noted that claim 8 improperly refers to canceled claim 2 and multiple dependent claim 4. These errors will be rectified at an appropriate time after the conclusion of this appeal.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.